U.S. Department of Health and Human Services
Food and Drug Administration

MEMORANDUM

Date: November 22, 2010

To: The Panel

Re: December 14-15 Meeting

The FDA is holding a meeting of the Dental Products Panel on December 14-15, 2010 to discuss issues related to the FDA's regulation of dental amalgam. The FDA has convened this meeting to solicit input from the panel on three topics: the best estimate for the level of exposure to mercury from dental amalgams; an appropriate reference exposure level (REL) for exposure to elemental mercury; and the findings from clinical studies of amalgam bearers.

BACKGROUND

Dental amalgam is a dental restorative material used to fill carious defects in teeth. It is a heterogenous intermetallic compound, consisting of liquid, elemental mercury and a powdered alloy composed of primarily silver, tin, and copper. Approximately 50% of dental amalgam is elemental mercury by weight. Dental amalgam has been on the U.S. market in its present form since the late 1800s. Over 50 million amalgam restorations are placed annually in the U.S[1]; however, use is decreasing. The two components of dental amalgam, mercury and amalgam alloy, were initially classified as separate devices in 1987. FDA issued a proposed rule to consolidate classification of dental mercury, amalgam alloy, and dental amalgam in 2002. A joint committee of CDRH Dental Products Panel and CDER Peripheral and Central Nervous System Drugs Advisory Committee met in 2006 to consider FDA's review of the most recent amalgam literature. That meeting identified gaps in the scientific knowledge, especially with respect to exposure limits and lack of attention to risk factors for sensitive subpopulations.

FINAL RULE

In 2009, FDA issued a final rule[2] reclassifying all components of dental amalgam into Class II (Special Controls) (21 CFR 872.3070) and issued a guidance document[3] as a special regulatory control. The classification regulation is as follows:

> § 872.3070 Dental amalgam, mercury, and amalgam alloy.

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[1] Beazoglu, T et al., Economic Impact of Regulating the Use of Amalgam Restorations, Public Health Reports, September-October 2007, Volume 122

[2] Final rule of August 4, 2009 (74 FR 38686)

[3] Guidance for Industry and FDA Staff, Class II Special Controls Guidance Document: Dental Amalgam, Mercury, and Amalgam Alloy, July 28, 2009.

(a) Identification. Dental amalgam is a device that consists of a combination of elemental mercury, supplied as a liquid in bulk, sachet, or predosed capsule form, and amalgam alloy composed primarily of silver, tin, and copper, supplied as a powder in bulk, tablet, or predosed capsule form, for the direct filling of carious lesions or structural defects in teeth. This device also includes the individual component devices, mercury and amalgam alloy, when intended to be combined with each other to form dental amalgam.

(b) Classification. Class II (special controls). The special control for this device is FDA's "Class II Special Controls Guidance Document: Dental Amalgam, Mercury, and Amalgam Alloy." See § 872.1(e) for the availability of this guidance document.

The guidance document includes recommendations for performance testing and a warning in labeling concerning the presence of mercury, but does not contain any warning concerning adverse health effects in the general population or in any subpopulation.

The basis for FDA's 2009 final rule was FDA's review of clinical literature and an assessment of the risk of mercury exposure from dental amalgam based on the U.S. Environmental Protection Agency's (EPA) Reference Concentration (RfC[4]) for chronic inhalation exposure to elemental mercury vapor (0.3 µg/m^3). The EPA RfC is based on several studies of exposure to elemental mercury, including studies of chloralkali workers. FDA prepared a review of clinical literature related to exposure to mercury from dental amalgam in a 2006 White paper, and an Addendum published in 2009.

PETITIONS

After the issuance of the final rule in 2009, FDA received four petitions requesting a reconsideration of the rule. Petitioners James Love, Jim Turner, and Richard Edlich, will be making presentations at the panel meeting of December 14-15, 2010. The petitioners raise several concerns, both scientific and administrative. Based on the concerns raised, the petitions requested that FDA either ban amalgam or place restrictions on its use, especially for pregnant women, children under six, and sensitive individuals. The petitions have been provided for you to review before the panel meeting.

Also presenting and available for questions will be Mark Richardson, PhD, of SNC- Lavalin Environment, formerly of Health Canada, whose published work is cited in James Love's petition dated September 3, 2009. Dr. Richardson will also discuss his ongoing work, supported by the petitioners, in the area of risk assessment of dental amalgam, which is not yet peer reviewed.

HOMEWORK ASSIGNMENT

[4] EPA defines a Reference Concentration (RfC) as follows: "An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL [No Observed Adverse Event Level], LOAEL [Lowest Observed Adverse Event Level], or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments " (http://www.epa.gov/ncea/iris/help_gloss.htm#r).

To enable the agency to consider critically the arguments raised by petitioners and whether they justify reconsideration of the final rule and FDA's regulatory approach, the FDA has prepared a "homework assignment" for three external experts (SGEs) on toxicology. The experts selected were:

William Farland, PhD. Dr. Farland is vice president for research at Colorado State University in Fort Collins, CO. He is also a professor in the Department of Environmental and Radiological Health Sciences, School of Veterinary Medicine and Biomedical Sciences. In 2006, Dr. Farland was appointed deputy assistant administrator for science in the US Environmental Protection Agency's (EPA) Office of Research and Development (ORD). He had served as the acting deputy assistant administrator since 2001. He served as EPA's acting Science Advisor throughout 2005. Formerly, he was the director of the ORD's National Center for Environmental Assessment (NCEA).
Dr. Farland holds a Ph.D. from UCLA in Cell Biology and Biochemistry**.**

Gary Ginsberg, PhD. Dr. Ginsberg is a toxicologist at the CT Dept. of Public Health within the Division of Environmental and Occupational Health Assessment. Dr. Ginsberg serves as adjunct faculty at the Yale School of Public Health and is an Assistant Clinical Professor at the University of Connecticut School of Medicine. He is a member of US EPA's Science Advisory Board and has served on USEPA's Children's Health Protection Advisory Committee (CHPAC). He received a Ph.D. in toxicology from the University of Connecticut and was a post-doctoral fellow in carcinogenesis/mutagenesis at the Coriell Institute for Medical Research. He has published in the areas of toxicology, carcinogenesis, physiologically-based pharmacokinetic modeling, inter-individual variability and children's risk assessment.

Robert Yokel, PhD. Robert A. Yokel, Ph.D. received his B.S. in Pharmacy from the University of Wisconsin in 1968 and Ph.D. from the University of Minnesota in Pharmacology in 1973. He has served a Director of Graduate Studies in Pharmaceutical Sciences and was Associate Dean for Research and Graduate Education in the College of Pharmacy for 7 years. Dr. Yokel's teaching has been in neuropharmacology and neurotoxicology, including metals. His research has focused on neurotoxic metals, their toxicokinetics and chelation, and recently the role of the physico-chemical properties of nanoscale materials in their kinetics and effects.

Each was asked a series of questions related to the risk assessment underlying the 2009 rule and the merits of other risk assessment approaches such as that of National Academy of Sciences. These experts will present their work at the December 14-15 meeting.

ADVISORY COMMITTEE MEETING

In addition, FDA has scheduled an advisory committee meeting on December 14-15, 2010, of the Dental Products Panel, supplemented with experts in toxicology, neurotoxicology, immunology, epidemiology, and pediatrics to discuss the merits of the petitioners concerns regarding the safety of dental amalgam. The format of the meeting will include presentations by FDA staff, the petitioners, Dr. Richardson, the three experts who completed the homework assignment; an open public hearing; FDA's questions to the panel; and a panel discussion.

FDA has scheduled this panel meeting to evaluate the scientific basis for FDA's 2009 regulation and whether a reevaluation of that rule is warranted. In particular, panel members will be asked to evaluate information relied upon by FDA and by the petitioners, analyses by outside experts in toxicology and risk assessment, and the scientific rationale underlying different approaches to risk assessment for dental mercury.

PANEL PACKAGE

To facilitate the panel's discussion the FDA is providing the following primary references:

- The 2009 Final Rule (review all, in particular Section I, Background)
- References to the Final Rule (review as needed)
- Four petitions (review all)
- Three responses to the homework (review all)
- An addendum will be provided with a list of speakers and the questions to the panel.

The following references are also provided, as they will be subject of panel questions and/or discussions:

- Special Controls Guidance (for specific performance testing and labeling)
- Mercury allergy and dental amalgam memo from CDER -,Division of Pulmonary, Allergy, and Rheumatology for a review of the mercury allergy literature)
- Mercury Exposure and Risks from Dental Amalgam, Parts 1 and 2, SNC-Lavilin Environment (for G. Mark Richardson's risk assessment)
- 2002 Proposed Rule (for background into earlier assessments)
- 2006 White Paper (for FDA review of the body of literature on amalgam)
- 2009 Addendum to White Paper (for updated FDA review on the body of literature on amalgam)
- Homework assignment questions and references (for original questions and Richardson et. al (2009) and Lettmeier et al. (2010) references)
- Presentations from the petitioners (draft)

OUTCOME

FDA is seeking the panel's input on the science underlying FDA's 2009 rule and the merits of the scientific arguments raised in the petitions. Specifically, FDA would like the panel to consider questions concerning the level of exposure to mercury from dental amalgams, the appropriate Reference Exposure Level to use in assessing the risk from dental amalgams, and what conclusions can be drawn from the body of clinical studies on dental amalgam. This information, together the findings of the experts asked to conduct homework assignments and the scientific literature relevant to the risks and benefits of dental amalgam, will be used by FDA in evaluating the 2009 rule and determining whether any changes to FDA's regulatory approach are warranted.